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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/783,391	02/20/2004	Pedro Aza-Blanc	P1111US10	6423

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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 08/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/783,391	AZA-BLANC ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *2-5,9 and 14-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-8 and 10-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/27/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-20 are all the pending claims for this application.

Election/Restrictions

2. Applicant's election without traverse of Group XXXIX (Claims 1, 6-8, 10-13) in the reply filed on July 26, 2005 is acknowledged.

3. Claims 2-5, 9, and 14-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected inventions.

4. Claims 1, 6-8 and 10-13 as drawn to methods for identifying JIK-modulating agents, are all the pending claims under examination.

Information Disclosure Statement

5. The non-patent literature reference cited in the IDS of June 27, 2005 has been considered and entered.

Claim Objections

6. Claims 6 and 7 are objected to for reciting non-elected subject matter for polypeptide modulators (i.e., genes of Table 2 except JIK (Claim 6) and the MIRSA and PLXNB1 genes (Claim 7)).

7. Claims 6 and 7 are objected to for reciting duplicate subject as being drawn to the JIK polypeptide modulator (due to the restriction, the gene is JIK and as such claims 6 and 7 are duplicates).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 7 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claim 1 is indefinite for the recitation "TRAIL" as the acronym encompasses an infinite number of proteins. Amending the claim to insert "TNF-related apoptosis-inducing ligand" would overcome the rejection.

b) Claim 1 is indefinite for the recitation "fragment" as it is unclear what portion of the JIK protein is contemplated. The specification teaches at [0040] "The fragments that can be employed in these assays usually retain one or more of the biological activities of the apoptosis-modulatory polypeptide (e.g., kinase activity if the apoptosis-modulatory employed in the first assaying step is a kinase)."

c) Claim 1 is indefinite in method step a) for the recitation "a biological activity of a polypeptide modulator" and because the elected gene is JIK, the claim encompasses any known or unknown biological activity for JIK. The only biological activity for JIK supported by the specification is kinase activity [0008, 0065].

d) Claim 1 is indefinite in method step b) for the recitation "modulate TRAIL-induced apoptosis" as it is unclear how this step would be performed. Is TRAIL-induced apoptosis measured in the same cell as the JIK kinase activity of step a)? Since many molecules are known to induce or are involved in pathways mediating apoptosis, how

does the method step discriminate between TRAIL-induced apoptosis versus any other molecule directly or indirectly involved? Does step b) involve mixing a test agent from step a) with a TRAIL molecule in the presence of a TRAIL-responsive cell line and measuring modulation of apoptosis? The specification teaches assays for analyzing apoptosis such as DNA fragmentation assay, assaying TRAIL-dependent caspase activation or cellular death [0069].

e) Claim 7 is indefinite for the recitation "JIK" as the acronym encompasses an infinite number of proteins. Amending the claim to insert "JNK inhibitory kinase" would overcome the rejection.

f) Claim 13 is indefinite for the recitation "assaying of the biological activity of the polypeptide modulator occurs in a cell", and as the elected claims are drawn to JIK, the phrase implies that a change in JIK activity would need to be visualized or detected by intracellular or in situ means. The specification teaches that the kinase activity of JIK can be assayed as described in the art, e.g., Tassi et al. J. Biol. Chem. 274:33287-95, 1999 [0065]. Tassi teaches HA-JIK transient transfection in COS7 cells, immunoprecipitation with anti-HA antibodies, and performing an immune complex kinase assay using myelin basic protein as an exogenous substrate. Tassi observed both autophosphorylation of JIK and MBP phosphorylation in vitro. Also, Examples 1 and 2 of the specification teach measuring siRNA inhibition of target RNA levels for JIK using quantitative PCR. Thus, neither of the disclosed methods are in situ means for measuring JIK biological activity.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 6-8, and 10-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a) screening a test agent in a bioassay measuring JIK kinase activity, b) screening a test agent in a bioassay measuring TRAIL-induced apoptosis, c) an RNAi-based loss of function screening method for identification of test agents/modulators of TRAIL-induced apoptosis in HeLa cells, d) identifying the JIK gene vis-à-vis the RNAi screening method with a JIK-specific RNAi test agent in HeLa cells, does not reasonably provide enablement for a test agent screening method comprising steps a) and b), using modulation of JIK bioactivity in the presence of a test agent as a correlate for TRAIL-induced apoptosis in any cell or cell line under just any conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

The claims are broadly drawn to screening for agents that modulate TRAIL-induced apoptosis comprising a two step method where step a) involves assaying the biological activity of the JIK protein (JNK/SAKP kinase inhibitor) in the presence of the agent and step b) involves assaying the agent for modulation of TRAIL-induced apoptosis in order to identify a TRAIL modulating agent, and further for step a) measuring kinase activity for JIK, measuring binding of the test agent to JIK, measuring modulation of the cellular level of JIK, and further for step b) measuring modulation of caspase activity, and where JIK kinase activity is measured in a cell.

Examples 1 and 2 of the specification and Aza-Blanc et al. (Molecular Cell 12:627-637 (2003); post-filing date publication by the instant inventors) teach a very specific method for identifying genes that effect (enhance/inhibit) TRAIL-induced apoptosis by screening HeLa cells using a siRNA directed against 510 genes including most kinases, i.e., JIK. To identify agents, the effects of the siRNA transfection on cell viability in the presence and absence of TRAIL was compared. For example, JIK-specific siRNA and relevant controls were transfected into HeLa cells in duplicate, and TRAIL was added to one cell group for an additional 24 hr period followed by cell viability measurement. The effect of siRNA on TRAIL-dependent death was calculated as the ratio of viability in the presence versus the absence of TRAIL. Transfection of JIK-specific siRNA into HeLa cells enhanced cell death in a TRAIL-dependent manner. Also, HeLa cells treated with JIK-specific siRNA showed TRAIL-dependent and –independent caspase activity, indicating that JIK has a more general anti-apoptotic role and that removing the biological activity (deleting the gene product) sensitizes cells to

TRAIL-induced death. The specification also teaches methods where biological activity monitored in the first screening step can be the specific biochemical or enzymatic activity of the apoptosis-modulatory polypeptide and that various assays for analyzing apoptosis are available for the second method step. The specification contemplates identifying any test agent defined as a protein, polypeptide, small organic molecule, polysaccharide, polynucleotide, and the like.

Applicants specification and the field of art do not draw a clear connection between the role of JIK and TRAIL in affecting apoptosis, and what if any correlative interpretation can be made in performing methods steps a) and b) to identify a test agent for the claimed intended use. While Applicant need not demonstrate how JIK affects TRAIL-induced apoptosis (*Parker v. Frilette*, 462 F.2d 544, 547, 174 USPQ 321, 324, (CCPA 1972), "an inventor need not understand precisely why his invention works in order to achieve an actual reduction to practice"), one skilled in the art would still be left to determine whether any test agent, e.g., JIK iRNA, identified through the method process would have a specific and substantial use in modulating TRAIL-induced apoptosis in any cell or cell line under any condition(s).

The interaction between JIK, JNK/SAPK and TRAIL appears to be a very complex relationship based on the literature. JIK regulates the JNK/SAPK pathway (Zhang et al. (Biochem Biophys Res Comm 274:872-879 (2000)) and JNK/SAPK activity contributes to TRAIL-induced apoptosis (Herr et al. Cell Death and Differentiation 6:130-135 (1999); hereinafter referred to as "Herr I") at least in some cells or cell lines. Herr I teaches that JNK/SAPK is activated in response to TRAIL in

leukemic T cell lines and "that activation of JNK/SAPK may contribute to apoptosis signaling downstream of death receptors. However, death signaling in lymphoid cell lines seems to differ from the pathway initiated in HeLa, 293 or MCF7 cells since in these systems a dichotomy upstream of FADD leading to JNK/SAPK activity was described." In other words, cross-linking of CD95 or TNF-R1 (TRAIL receptor) in HeLa, 293 or MCF7 cells engages a pathway distinct from the pathway (the FADD/FLICE/caspases pathway) leading to JNK/SAPK activation in leukemic T cells.

Further, Herr et al. (Int. J. can. 80:417-424 (1999); hereinafter referred to "Herr II") teaches that activation of JNK/SAPKs in response to cellular stress (TRAIL) is not strictly associated with signaling through death receptors involved in induction of apoptosis in leukemia T cell lines (p. 417, Col. 1). Herr II teaches that the role of JNK/SAPK activity during cellular stress-induced apoptosis is not entirely clear and that activation of JNK/SAPK contributes to the cell death program initiated by cellular stress-induced apoptosis, e.g., serving as a sensitizer which may be required, but is not sufficient for induction of death. (p. 423, Col. 2, ¶3). It is noteworthy that the Examiner was not able to identify any references describing an inherent or implied relationship between JIK and TRAIL-induced apoptosis. Inasmuch as multiple signaling pathways and cell type-specific variations contribute to the targeted regulation of TRAIL-induced apoptosis, neither a specific or substantial role for JIK or JNK/SAPK has been established in a number of different cell lines, most significantly, HeLa cells.

Thus it follows that with the role of the natural substrate for JIK, JNK/SAPK, being questionable (or even less than substantial) in affecting TRAIL-induced apoptosis,

and that no other correlation is known to exist between JIK and TRAIL, then one of skill in the art could not rely on method step a) as being predictive of whether any test agent was modulatory for TRAIL-induced apoptosis.

Additionally, Applicant's specification and Aza-Blanc et al. (p. 631, Col. 1, ¶3) both caution that "one potential concern in using siRNAs for phenotypic screens is that since siRNAs are not 100% selective for the intended mRNA target the observed phenotype could be due to inhibition of either the intended target or an off-target mRNA." It is apparent that in practicing the claimed method invention, one of skill in the art would need to be apprised of the non-specificity for some iRNAs in the targeting method and that performing numerous specific controls would be required to practice method steps a) and b).

Thus, without there being a clear correlation between JIK kinase activity and TRAIL-induced apoptosis, the intended application(s) or uses of the screening method for identifying a specific and substantial test agent is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).

The combined art disclosure of Zhang, Herr I and Herr II is dispositive to there being a strong correlation for JIK activity and TRAIL-induced apoptosis as is required for the claimed method. One of skill in the art could not practice the method with a reasonable expectation of success, absent examples providing evidence, which is

reasonably predictive for the breadth of the claimed method steps a) and b) in any cell or cell type, and the enablement provided by the specification is not commensurate in scope with the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

A. Rejection of Claims for Method Step a) (based on enablement rejection for two step method, see section 9 supra)

10. Claims 1 and 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Tassi et al. (J Biol Chem 274: 33287-95, 1999); hereinafter referred to as "Tassi") as applied to step a) of the method claims.

Claims 1 and 6-8 are drawn to a method for identifying test agents that modulate a biological activity of JIK protein, where the activity is kinase activity.

Tassi discloses pCEFL-HA-JIK or pCEFL-HA-JIKA vectors encoding the kinase-active JIK protein (p.33288, Col. 2, ¶4), transfecting COS7 cells with the vectors, stimulating cells with epidermal growth factor (EGF), and performing an extracellular kinase assay using GST-ATF2 fusion protein or myelin basic protein as substrate.

Applicants are reminded that because the claims are drawn to any test agent and assaying any biological activity for JIK, that an assay for JIK-mediated auto-phosphorylation or phosphorylation of another substrate induced by EGF test agent, is encompassed by the claims, and therefore anticipated by Tassi.

11. Claims 1 and 6-8 are rejected under 35 U.S.C. 102(a) as being anticipated by De Souza et al. (Blood 99:3432-3438 (May 1, 2002); hereinafter referred to as "De Souza") as evidenced by Human Protein Reference Database (see output for TAO kinase 3 listing Ste20 like kinase as a synonym for JIK; hereinafter referred to as "HPRD") and as applied to step a) of the method claims.

The interpretation of Claims 1 and 6-8 is discussed supra.

De Souza discloses the role of Mst 1 (Ste20 like kinase) in mediating eosinophil apoptosis, and as evidenced by HPRD, Ste20 like kinase is synonymous with JIK. De Souza discloses suppression of Mst1 kinase activity with the caspase inhibitor, z-Asp-CH2-DCB (Figure 5), and upregulation of Mst1 kinase activity with Fas/CD95-activating antibody, CH-11 (Figure 6), using an "in gel" renaturation assay (p. 3434, Col. 1, ¶4).

Applicants are reminded that because the claims are drawn to any test agent and assaying any biological activity for JIK, that an assay for modulating JIK (or Mst1 or Ste20 like kinase)-mediated phosphorylation of another substrate by test agent such as z-Asp-CH2-DCB or CH-11, is encompassed by the claims, and therefore anticipated by De Souzaas evidenced by HPRD.

B. Rejection of Claims for Method Step b) (based on enablement rejection for two step method, see section 9 supra)

12. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Weldon et al. (Surgery 132:293-301 (August 2002); hereinafter referred to as "Weldon"; cited in the IDS of June 27, 2005) as applied to method step b).

Claim 1 is drawn to a method for identifying test agents that modulate TRAIL-induced apoptosis.

Weldon discloses blocking TRAIL-induced cytotoxicity in Apo cells with the known cell survival signaling compound, PMA, where cell viability was measured by mean relative light units (Figure 5) (p. 300, Col. 1, ¶3).

Applicants are reminded that because the claims are drawn to any test agent and assaying any modulation of TRAIL-induced apoptosis, that an assay measuring cell viability in the presence of TRAIL and test agent PMA, is encompassed by the claims, and therefore anticipated by Weldon.

13. Claims 1 and 12 are rejected under 35 U.S.C. 102(a) as being anticipated by Cantarella et al. (Cell Death and Differentiation 10:134-141 (January 2003); hereinafter referred to as "Cantarella") as applied to method step b).

The interpretation of Claim 1 is discussed supra. Claim 12 is drawn to testing agents for caspase activity modulation.

Cantarella discloses beta amyloid protein (βAP) induction of TRAIL induced apoptosis in the neuronal SH-SY5Y cell line, and blocking the effect of βAP cytotoxicity

with a TRAIL-neutralizing monoclonal antibody. Thus, Cantarella discloses two different test agents for modulating TRAIL-induced apoptosis. Cantarella discloses that "binding of TRAIL to its death domain receptors lead to activation of caspase-8, with subsequent activation of caspase 3, finally resulting in apoptosis" (p. 137, Col. 1, ¶1). Cantarella teaches adding a caspase-8 inhibitor, z-IETD-FMK, to SH-SY5Y cultures in the presence of βAP reduces both βAP- and TRAIL-induced neurotoxicity by 70% (Figure 7).

Applicants are reminded that because the claims are drawn to any test agent and assaying any modulation of TRAIL-induced apoptosis and caspase activity modulation, that an assay measuring cell viability in the presence of a test agent βAP with or without a second test agent, TRAIL Mab, and further measuring caspase activity with a test agent, z-IETD-FMK, that also modulates TRAIL activity, is encompassed by the claims, and therefore anticipated by Cantarella.

Conclusion

14. No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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